

II. Remarks/ Arguments

Reconsideration of the application in view of the above amendments and the following remarks is requested.

Claims 1, 4, 7-8, 12-16, 57-60, and 69 are pending in the applications. Claims 1, 4, 8, and 69 are independent.

Claims 1, 4, 7-8, 12-16, 57-60, and 69 were rejected under 35 U.S.C. § 112, first paragraph, written description requirement, for the reasons discussed on pages 3-4 of the Office Action. Applicants respectfully traverse this rejection on the ground that the person of ordinary skill in the art would readily apprehend that Applicants were in possession of the claimed invention as of the application filing date. Nevertheless, solely to advance this application to issue, Applicants have amended the claims to remove any reference to the term “prodrug.”

Claims 1, 4, 7-8, 12-16, 57-60, and 69 were rejected under 35 U.S.C. § 112, first paragraph, enablement requirement, for the reasons discussed on pages 4-6 of the Office Action. Applicants respectfully traverse this rejection on the ground that the person of ordinary skill in the art would be readily enabled to make and use the invention given the specification and Drawings, without undue experimentation. The Examiner states that the Applicants have not provided the necessary direction such that one of skill in the art would be able to use CR4, or any of the other non-elected compounds, in order to treat an animal for cancer.

The Examiner specifically states that claims 57-60 claim treatment of animals which are “at risk for developing vascularised solid tumor”, but that the Applicants have not defined how one of skill in the art would know who is at risk. Further, the Examiner states that it is not shown how to prevent the disease by treating those who are merely at risk, before they develop it.

Applicants respectfully submit that a person skilled in the art would know who is “at risk for developing vascularised solid tumor”. Further, Applicants submit that information is available that provides a person with such information, for example the National Cancer Institute publishes information pertaining to risk factors for different types of cancer. It is well known that risk factors for breast cancer include mutations in the BRCA1 or BRCA2 genes (Bishop DT, Eur. J. Cancer. 1994, 30A(12):1738-39), family history of disease, prior clinical incidence and age (<http://www.cancer.gov/cancertopics/pdq/genetics/breast-and->

ovarian/HealthProfessional/page2 attached hereto). Similar guidelines are also provided for prostate cancer and melanoma, see ([http://www.cancer.gov/cancertopics/pdq/genetics/prostate/Health Professional/page6](http://www.cancer.gov/cancertopics/pdq/genetics/prostate/HealthProfessional/page6), and <http://www.cancer.gov/cancertopics/pdq/screening/skin/HealthProfessional/page3> both attached hereto). Applicants respectfully submit that a person skilled in the art, having access to this information, would be able to assess who is “at risk for developing vascularised solid tumor”.

The Examiner further states that “Applicants have only shown cell culture data, and has not shown treating affected patients or shown an art recognized correlation between the data shown and the scope of the claimed invention”. The Examiner states that there is “merely an unsubstantiated assertion with no evidence to support the contention that the *in vitro* studies of the specification are indicative of *in vivo* activity.”

Applicants respectfully disagree with the Examiner. As indicated by the Examiner, Applicants have provided *in vitro* data showing the inhibition of VEGF, by the compounds of interest, in 3 breast cancer cell lines (HTB-133, HTB-131 and MDA-231), prostate cancer cell line (HTB-181), melanoma cell line (HTB-72) and human umbilical vascular endothelial cell line (CR2-1730).

Applicants respectfully submit that these cell lines are known cell lines that are used in the art, including for the identification of anticancer drugs. With respect to the elected disease breast cancer, Applicants respectfully submit that the MDA-231 cells are commonly used to screen for anticancer drugs that will be effective against breast cancer. For example, the US National Cancer Institute operates a service for the cancer research community in which they utilize 60 tumor cell lines (NCI60) representing various types of cancer to screen for anticancer drugs <http://dtp.nci.nih.gov/screening.html> (attached). The MDA-231 cell line is one of the NCI60 cell lines used as representative of breast cancer http://dtp.nci.nih.gov/docs/misc/common_files/cell_list.html (attached). Therefore, the NCI is using MDA-231 cells for *in vitro* drug screens to identify anticancer drugs.

The specification also includes the HTB-133 breast cancer cell line and a VEGF-receptor negative variant of that cell line, HTB-131. Applicants respectfully submit that the demonstration of CR4 activity in multiple breast cancer cell lines, as opposed to only one, further enforces the predictive value of the *in vitro* tests for *in vivo* anticancer activity.

Applicants respectfully submit that the information provided demonstrates that these cell lines are known and are used in the art and that a person skilled in the art would recognise that the *in vitro* data and results provided are indicative of the claimed *in vivo* subject matter. Therefore, Applicants submit that sufficient teaching has been provided to allow one to have a reasonable expectation of success in transferring the *in vitro* method to treat affected patients. Any requirement to supply specific *in vivo* data places an unnecessary burden on the Applicants and any amendment in the claims to include reference to “*in vitro*” methods would unfairly restricts the scope of Applicants’ claims.

Claim Rejections- 35 U.S.C. §103(a)

The Examiner has rejected claims 1, 4, 7-8, 12-16, 57-60 and 69 under 35 U.S.C. 103(a) as being unpatentable over Roifman et al. (WO 01/79158 A2) in view of Bessette et al. (US 2003/0017215 A1) in further view of Butler et al. (US 5,486,457). The Examiner states that it would have been obvious to one of ordinary skill in the art at the time of the invention that the method of Roifman et al. would be useful for breast cancer in addition to the cancers named as the compounds are shown to inhibit cell proliferation and cell proliferation is also linked to breast cancer.

Applicants respectfully disagree that the subject matter of the pending claims is obvious in light of the cited references.

The pending claims are directed to a method of inhibiting secretion of vascular endothelial growth factor in an animal, a method of inhibiting an effect of vascular endothelial growth factor in an animal in need of such inhibition and a method of treating a disorder caused or contributed to by vascular endothelial growth factor in an animal. The pending claims are all related to the inhibition of vascular endothelial growth factor (VEGF). As stated in the Summary of the Invention section, the present application is directed to the “unexpected discovery” that certain compounds are capable of inhibiting the activity of VEGF. In addition, *in vitro* data is provided to show that the exemplified compounds inhibit VEGF secretion, see Examples 15-18.

Applicants respectfully submit that there is no teaching or suggestion, in any of the cited references, of the specific use of these compounds for the inhibition of VEGF. Therefore, although as stated the by the Examiner, Roifman teaches, for example, the structure of CR4,

there is no discussion of the use of CR4 for the inhibition of VEGF. In addition, there is no specific discussion of VEGF in either Bessette et al. or Butler et al.. Applicants therefore, respectfully submit that a person skilled in the art, given the teachings in the cited art, would not be led to the subject matter of the pending claims. Withdrawal of this objection is respectfully requested.

In view of the above remarks, and amendments submitted herewith, Applicants respectfully submit that independent amended claims 1, 4, and 8 are novel and inventive over the cited art. Further, as the remaining dependent claims are dependent on these independent claims, Applicants similarly respectfully submit that these claims are novel and inventive over the cited art. Applicants respectfully request reconsideration and allowance of the application.

If the Examiner has further concerns, he is encouraged to contact Applicants' undersigned agent if the Examiner considers that a telephone conference would be of assistance in this matter.

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Respectfully submitted,

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Genetics of Breast and Ovarian Cancer (PDQ®)



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General Information

Â [Note: Many of the medical and scientific terms used in this summary are found in the [NC Genetics Terms](#). When a linked term is clicked, the definition will appear in a separate window.]

Among women, breast cancer is the most commonly diagnosed cancer after nonmelanoma and is the second leading cause of cancer deaths after lung cancer. In 2008, an estimated 292,700 cases will be diagnosed, and 40,480 deaths from breast cancer will occur.[1] The incidence of breast cancer, particularly for estrogen receptor-positive cancers occurring after age 50 years, has increased since 2003; this may be temporally related to a decrease in hormone replacement therapy following early reports from the Women's Health Initiative.[2] Ovarian cancer is the eighth most common cancer, with an estimated 21,650 new cases in 2008, but is the fifth most deadly, with an estimated 15,520 deaths in 2008.[1] (Refer to the PDQ summary on [Breast Cancer Treatment and Management](#) for more information on breast cancer and ovarian cancer rates and management.)

A possible genetic contribution to both breast and ovarian cancer risk is indicated by the increased incidence of these cancers among women with a [family history](#) (see the [Family History as a Risk Factor for Breast Cancer](#) and the [Family History as a Risk Factor for Ovarian Cancer](#) sections below), observation of rare families in which multiple family members are affected with breast and/or ovarian cancer, in a pattern compatible with autosomal dominant inheritance of cancer susceptibility genes. Studies of families (linkage analysis) have subsequently proven the existence of autosomal predispositions to breast and ovarian cancer and have led to the identification of several high-risk genes as the cause of inherited cancer risk in many cancer-prone families. (Refer to the [PDQ Cancer Genetics Overview](#) for more information on linkage analysis.) [Mutations](#) in these genes

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the general population and are estimated to account for no more than 5% to 10% of breast cancer cases overall. It is likely that other genetic factors contribute to the etiology of some cancers.

Family History as a Risk Factor for Breast Cancer

In cross-sectional studies of adult populations, 5% to 10% of women have a mother or sister with breast cancer, and about twice as many have either a first-degree relative or a second-degree relative with breast cancer.[3-6] The risk conferred by a family history of breast cancer has been assessed in both case-control and cohort studies, using volunteer and population-based samples, with generally consistent results. In a pooled analysis of 38 studies, the relative risk (RR) of breast cancer conferred by a first-degree relative with breast cancer was 2.1 (95% confidence interval [CI], 2.0-2.2).[7] Risk increases with the number of first-degree relatives and age at diagnosis.[4,5,7] Refer to the [Penetrance of Mutations](#) section for a discussion of the familial risk for women from families with *BRCA1/2* mutations who themselves test negative for a mutation.

Family History as a Risk Factor for Ovarian Cancer

Although reproductive, demographic, and lifestyle factors affect risk of ovarian cancer, the strongest risk factor is a family history of the disease. A large meta-analysis of 15 published studies estimated an odds ratio (OR) of 3.1 for the risk of ovarian cancer associated with at least one first-degree relative with ovarian cancer.[8]

Autosomal Dominant Inheritance of Breast/Ovarian Cancer Predisposition

Autosomal dominant inheritance of breast/ovarian cancer is characterized by transmission of the predisposition from generation to generation, through either the mother's or the father's family, with the following characteristics:

- Inheritance risk of 50%. When a parent carries an autosomal dominant genetic predisposition, each child has a 50:50 chance of inheriting the predisposition. Although the risk of inheriting the predisposition is 50%, not everyone with the predisposition will develop cancer because of incomplete penetrance and/or gender-restricted or gender-related expression.
- Both males and females can inherit and transmit an autosomal dominant cancer predisposition. A person who inherits a cancer predisposition and shows no evidence of it can still pass the allele to his or her sons and daughters.

Breast and ovarian cancer are components of several autosomal dominant cancer predisposition syndromes. The most strongly associated with both cancers are *BRCA1* or *BRCA2* mutation syndromes. Breast cancer is also a common feature of [Li-Fraumeni syndrome](#) due to *TP53* mutations; of [Cowden syndrome](#) due to *PTEN* mutations; and with mutations in *CHEK2*. [9] Other genetic syndromes that may include breast cancer as an associated feature include heterozygous carriers of the [ataxia telangiectasia](#) gene and [Peutz-Jeghers syndrome](#). Ovarian cancer has also been associated with [Lynch syndrome](#) (Gorlin) syndrome (OMIM), and multiple endocrine neoplasia type 1 (MEN1) (OMIM). Each of these genes produces different clinical phenotypes of characteristic malignancies and, in some instances, associated nonmalignant abnormalities.

The family characteristics that suggest hereditary breast and ovarian cancer predisposition are the following:

- Cancers typically occur at an earlier age than in [sporadic](#) cases (defined as cases not associated with a known genetic risk).
- Two or more primary cancers in a single individual. These could be multiple primary cancers of the same type (e.g., bilateral breast cancer) or primary cancer of different types (e.g., breast and colorectal cancer in the same individual).
- Cases of male breast cancer.
- Possible increased risk of other selected cancers and benign features for males and females. Refer to the [Major Genes](#) section of this summary for more information.)

There are no pathognomonic features distinguishing breast and ovarian cancers occurring in *BRCA2* mutation carriers with those occurring in noncarriers. Breast cancers occurring in *BRCA2* carriers are more likely to be estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, HER2/neu receptor-negative and have a basal phenotype. *BRCA1*-associated ovarian cancers are more likely to be of mucinous or borderline histopathology. [Refer to the [Pathology/Prognosis of Breast Cancer](#) and [Pathology/Prognosis of Ovarian Cancer](#) sections for more information.]

Difficulties in Identifying a Family History of Breast and Ovarian Cancer

When using family history to assess risk, the accuracy and completeness of family history must be taken into account. A reported family history may be erroneous, or a person may be unaware of being affected with cancer. In addition, small family sizes and premature deaths may limit the information obtained from a family history. Breast or ovarian cancer on the paternal side of the family may be more distant relatives than on the maternal side and thus may be more difficult to obtain. When compared with self-reported information with independently verified cases, the sensitivity of a history of breast cancer is relatively high, at 83% to 97%, but lower for ovarian cancer, at 60%. [10,11]

Other Risk Factors for Breast Cancer

Other risk factors for breast cancer include age, reproductive and menstrual history, hormonal therapy, radiation exposure, mammographic breast density, alcohol intake, physical activity, anthropometric variables, and a history of benign breast disease. (Refer to the PDQ summary on [Breast Cancer Prevention](#) for more information.) These factors are considered in more detail in numerous reviews including among *BRCA1/BRCA2* mutation carriers. [14] Brief summaries are given below, highlighting where possible, the effect of these risk factors in women who are genetically susceptible to breast cancer. (More information about their effects in *BRCA1/BRCA2* mutation carriers can be found in the [Interventions](#) later in this document.)

Age

Cumulative risk of breast cancer increases with age, with most breast cancers occurring after age 50. [15] In women with a genetic susceptibility to breast cancer, and to a lesser degree, ovarian cancer, the risk of cancer occurs at an earlier age than in sporadic cases.

Reproductive and menstrual history

Breast cancer risk increases with early menarche and late menopause, and is reduced by early term pregnancy. Although results have been complex and may be gene dependent, several studies have suggested that the influence of these factors on risk in *BRCA1/BRCA2* mutation carriers appears similar to noncarriers. [14,16]

Oral contraceptives

Oral contraceptives may produce a slight increase in breast cancer risk among long-term users, but this appears to be a short-term effect. In a meta-analysis of data from 54 studies, the risk of breast cancer associated with oral contraceptive use did not vary according to a family history of breast cancer. [17]

Oral contraceptives are sometimes recommended for ovarian cancer prevention in *BRCA1/BRCA2* mutation carriers, but studies of their effect on breast cancer risk have been inconsistent. [18]

Hormone Replacement Therapy

Data exist from both observational and randomized clinical trials regarding the association between postmenopausal hormone replacement therapy (HRT) and breast cancer. A meta-analysis of observational studies indicated a RR of breast cancer of 1.35 (95% CI, 1.21-1.49) for women who used HRT for 5 or more years after menopause. [21] The Women's Health Initiative (WHI), a large randomized controlled trial of about 160,000 postmenopausal women, investigated the risks and benefits of the estrogen-plus-progestin arm of the study, which randomized more than 16,000 women to receive HRT or placebo, was halted early because health risks exceeded benefits. [22,23] Adverse effects prompting closure included significant increase in both total (245 vs. 185 cases) and invasive (152 vs. 102 cases) breast cancers (RR = 1.24; 95% CI, 1.02-1.5, $P < .001$) and increased risks of coronary heart disease, stroke, and pulmonary embolism. Similar findings were seen in the estrogen-progestin only arm of the study. [24]

prospective observational Million Women[®]s Study in the United Kingdom.[24] The risk was not elevated, however, in women randomly assigned to estrogen-only versus placebo (RR = 0.77; 95% CI, 0.59–1.01). Eligibility for the estrogen-only arm of this study required and 40% of these patients also had undergone oophorectomy, which potentially could have breast cancer risk.[25]

The association between HRT and breast cancer risk among women with a family history of breast cancer has not been consistent; some studies suggest risk is particularly elevated among women with a family history, while others have not found evidence for an interaction between these factors.[26–32] The increased risk of breast cancer associated with HRT use in the large meta-analysis did not differ significantly between subjects with and without a family history. The WHI study has not been stratified on breast cancer family history, and subjects have not been systematically tested for BRCA1 or BRCA2 mutations.[23] Short-term use of hormones for treatment of menopausal symptoms appears to have little or no breast cancer risk.[21,31] The effect of HRT on breast cancer risk among carriers of BRCA1 or BRCA2 mutations has been studied only in the context of bilateral risk-reducing oophorectomy. Short-term replacement does not appear to reduce the protective effect of oophorectomy or risk.[32]

Radiation exposure

Observations in survivors of the atomic bombings of Hiroshima and Nagasaki and in women who received therapeutic radiation treatments to the chest and upper body document increased risk as a result of radiation exposure. The significance of this risk factor in women with a genetic susceptibility to breast cancer is unclear.

Preliminary data suggest that increased sensitivity to radiation could be a cause of cancer in carriers of BRCA1 and BRCA2 mutations,[33–36] and in association with germline ATM and TP53 mutations.[37,38] Since BRCA1/2 mutation carriers are heterozygotes, however, radiation sensitivity occurs only after a somatic mutation has damaged the normal copy of the gene.

The possibility that genetic susceptibility to breast cancer occurs via a mechanism of radiation sensitivity raises questions about radiation exposure. It is possible that diagnostic radiation exposure, such as mammography, poses more risk in genetically susceptible women than in women of average risk. Therapeutic radiation could also pose carcinogenic risk. A cohort study of BRCA1 and BRCA2 mutation carriers treated with breast-conserving therapy, however, showed no evidence of increased sensitivity or sequelae in the breast, lung, or bone marrow of mutation carriers.[39] Conversely, radiation sensitivity could make tumors in women with genetic susceptibility to breast cancer more responsive to radiation treatment. Studies examining the impact of mammography and chest x-ray exposure in BRCA1 and BRCA2 mutation carriers have had conflicting results.[40,41] (Refer to text on [Radiation Therapy](#) section of this summary for more information.)

Alcohol intake

The risk of breast cancer increases by approximately 10% for each 10g of daily alcohol intake (approximately 1 drink or less) in the general population.[42,43] One study of BRCA1/BRCA2 mutation carriers found no increased risk associated with alcohol consumption.[44]

Physical Activity and Anthropometry

Weight gain and being overweight are commonly recognized risk factors for breast cancer. In the general population, overweight women are most commonly observed to be at increased risk of postmenopausal breast cancer and at reduced risk of premenopausal breast cancer. Sedentary lifestyle may also be a risk factor. These factors have not been systematically evaluated in women with a positive family history of breast cancer or in carriers of cancer-predisposing mutations, but one study suggested a reduced risk associated with exercise among BRCA1 and BRCA2 mutation carriers.[46]

Benign breast disease and mammographic density

Benign breast disease (BBD) is a risk factor for breast cancer, independent of the effects of other risk factors for breast cancer (age, age at menarche, age at first live birth, and family history of breast cancer).[47] There may also be an association between benign breast disease and family history of breast cancer.[48]

An increased risk of breast cancer has also been demonstrated for women who have increased breast tissue as assessed by mammogram,[47,49,50] and breast density may have a genetic etiology.[51-53]

Other factors

Other risk factors, including those that are only weakly associated with breast cancer and that have been inconsistently associated with the disease in epidemiologic studies (e.g., cigarette smoking), are important in subgroups of women defined according to genotype. For example, some studies have suggested that certain N-acetyl transferase alleles may influence female smokers' risk of breast cancer.[54] One study [55] found a reduced risk of breast cancer among *BRCA1/2* mutation carriers who smoked, but an expanded follow-up study failed to find an association.[56]

Other Risk Factors for Ovarian Cancer

Factors that increase risk for ovarian cancer include increasing age and nulliparity, while factors that decrease risk include surgical history and oral contraceptives.[57,58] (Refer to the PDQ summary on Prevention of Ovarian Cancer for more information.) Relatively few studies have addressed these risk factors in women who are genetically susceptible to ovarian cancer. (Refer to the Genetic Modification section for more information.)

Age

Ovarian cancer incidence rises in a linear fashion from age 30 years to age 50 years and continues to increase, though at a slower rate, thereafter. Before age 30 years, the risk of developing ovarian cancer is remote; even in hereditary cancer families.[59]

Reproductive history

Nulliparity is consistently associated with an increased risk of ovarian cancer, including among *BRCA1/BRCA2* mutation carriers.[60] Risk may also be increased among women who have used oral contraceptives, especially those who remain nulligravid.[57,61] Evidence is growing that the use of oral contraceptives is associated with an increased risk of ovarian cancer, particularly in long-time users and with sequential estrogen-progesterone schedules.[62-65]

Surgical history

Bilateral tubal ligation and hysterectomy are associated with reduced ovarian cancer risk,[57] including in *BRCA1/BRCA2* mutation carriers.[68] Ovarian cancer risk is reduced more than in the general population with documented *BRCA1* or *BRCA2* mutations who chose risk-reducing salpingo-oophorectomy. In this same population, prophylactic removal of the ovaries also resulted in a nearly 50% reduction in the risk of subsequent breast cancer.[69,70] For further information on these studies refer to the [Risk-Reducing Salpingo-Oophorectomy](#) section of this summary.

Oral contraceptives

Use of oral contraceptives for 4 or more years is associated with an approximately 50% reduction in ovarian cancer risk in the general population.[57,58] A majority of, but not all, studies also support oral contraceptives being protective among *BRCA1/BRCA2* mutation carriers.[60,71-74]

Models for Prediction of Breast Cancer Risk

Models to predict an individual's lifetime risk for developing breast cancer are available. Several models exist to predict an individual's likelihood of having a *BRCA1* or *BRCA2* mutation. For information on these models refer to the Models for Prediction of the Likelihood of a *BRCA1* or *BRCA2* Mutation section of this summary. Not all models can be appropriately applied for all patients; a model is appropriate only when the patient's characteristics and family history are similar to the population on which the model was based. The table, [Characteristics of the Gail and Claus Models](#), summarizes the salient aspects of the risk assessment models and is designed to aid in choosing the model that best applies to a particular individual.

Two models for predicting breast cancer risk, the Claus model [75,76] and the Gail model,[77] are used in research studies and clinical counseling. Both have limitations, and the risk estimates from the two models may differ for an individual patient. These models, however, represent the best currently available for individual risk assessment.

It is important to note that these models will significantly underestimate breast cancer risk for families with hereditary breast cancer susceptibility syndromes. In those cases, Mendelian inheritance models apply. A 3-generation cancer family history is taken before applying any model. (Refer to the section on [Cancer Genetics Risk Assessment and Counseling](#) for more information on [Taking a Family History](#).) Generally, the Claus or Gail models should not be the sole model used for families with one or more of the following characteristics:

- Three individuals with breast or ovarian cancer (especially when one or more breast cancers were diagnosed before age 50 years).
- A woman who has both breast and ovarian cancer.
- [Ashkenazi Jewish](#) ancestry with at least one case of breast or ovarian cancer (as these individuals are more likely to have a hereditary cancer susceptibility syndrome).

Table 1. Characteristics of the Gail and Claus Models^a

	Gail Model	Claus Model
Data derived from	Breast Cancer Detection Demonstration Project (BCDDP) Study	Cancer and Steroid Hormone Study
Study population	2,852 cases, aged 20-35 years	4,730 cases, aged 20-35 years
	<i>In situ</i> and invasive cancer	Invasive cancer
	3,146 controls	4,688 controls
	Caucasian	Caucasian
	Annual breast screening	Not routinely screened
Family history characteristics	First-degree relatives with breast cancer	First-degree or second-degree relatives with breast or ovarian cancer
		Age of onset in relatives
Other characteristics	Current age	Current age
	Age at menarche	
	Age at first live birth	
	Number of breast biopsies	
	Atypical hyperplasia in breast biopsy	
	Race (included in the most current version of the Gail model)	
Strengths	Incorporates:	Incorporates:
	Risk factors other than family history	Paternal as well as maternal family history
		Age at onset of breast or ovarian cancer
		Family history of ovarian cancer
Limitations	Underestimates risk in hereditary families	May underestimate risk in hereditary families
	Number of breast biopsies without atypical hyperplasia may cause inflated risk estimates	May not be applicable to all combinations of affected relatives
		Does not include risk from paternal family history
	Does not incorporate:	
	Paternal family history of breast cancer or any family history of ovarian cancer	

	Age at onset of breast cancer in relatives	
	All known risk factors for breast cancer [80]	
Best application	For individuals with no family history of breast cancer or 1 first-degree relative with breast cancer, aged ≥ 50 years	For individuals with degree or second-degree breast cancer
	For determining eligibility for chemoprevention studies	
^a Adapted from Domchek et al.,[78] Rubenstein et al.,[79] and Rhodes.[80]		

The Gail model has been found to be reasonably accurate at predicting breast cancer risk in white women who undergo annual screening mammography.[81-85] While the model is useful for predicting the number of breast cancer cases expected in a group of women from the same age group, it is less reliable in predicting risk for individual patients. Risk can be overestimated in:

- Nonadherent women (i.e., does not adhere to screening recommendations).[81,82]
- Women in the highest risk strata.[84]

Risk could be underestimated in the lowest risk strata.[84] Earlier studies [81,82] suggested overprediction in younger women and underprediction in older women. More recent studies of the modified Gail model (which is currently used) found it performed well in all age groups. Further studies are needed to establish the validity of the Gail model in minority populations.[85]

A study of 491 women aged 18 to 74 years with a family history of breast cancer compared the Gail model to the Claus model in predicting breast cancer risk.[86] The two models were poorly correlated ($r = .55$). The Gail model estimates were higher than the Claus model estimates for most participants. Presentation and discussion of both the Gail and Claus models risk estimates are available in the counseling setting.

The Gail model is the basis for the Breast Cancer Risk Assessment Tool, a computer program available from the NCI by calling the Cancer Information Service at 1-800-4-CANCER (1-800-4-CANCER TTY at 1-800-332-8615). This version of the Gail Model estimates only the risk of invasive breast cancer.

The Tyrer-Cuzick model incorporates both genetic and non-genetic factors.[87] A three-generation pedigree is used to estimate the likelihood that an individual carries either a *BRCA1/BRCA2* mutation or a hypothetical low penetrance gene. In addition, the model incorporates personal risk factors: body mass index, height, and age at menarche, menopause and first live birth. Both genetic and nongenetic factors are combined to develop a risk estimate. Although powerful, the model is less accessible to primary care providers than the Gail and Claus models. The BOADICEA model examines family history to estimate breast cancer risk, and also incorporates both *BRCA1/BRCA2* genetic risk factors.[88]

Other models incorporating breast density have been developed, but are not ready for clinical use. In the future, models may be developed or refined to include such factors as breast density and biomarkers.

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Genetics of Prostate Cancer (PDQ®)



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NCI Highlights

Prostate Cancer Risk Assessment

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The purpose of this section is to describe current approaches to assessing and counseling patients about susceptibility to prostate cancer. Genetic counseling for men at increased risk of prostate cancer encompasses all of the elements of genetic counseling for other hereditary cancers. (Refer to the PDQ summary on [Cancer Genetics Risk Assessment and Counseling](#) for more information.) The components of genetic counseling include concepts of risk for prostate cancer, reinforcing the importance of detailed family history, pedigree analysis to derive age-related risk, and offering participation in research studies to those individuals who have multiple affected family members.[1,2] Genetic testing for prostate cancer susceptibility is not available outside of the context of a research study. Families with prostate cancer can be referred to ongoing research studies; however, these studies will not provide individual genetic results to participants.

Prostate cancer will affect an estimated 1 in 6 American men over their lifetime. Currently, evidence exists to support the hypothesis that approximately 5% to 10% of all prostate cancer is due to rare autosomal dominant prostate cancer susceptibility genes.[3,4] The proportion of prostate cancer associated with an inherited susceptibility may be even larger.[5-7] Men are generally considered to be candidates for genetic counseling regarding prostate cancer risk if they have a family history of prostate cancer. The Hopkins Criteria provide a working definition of hereditary prostate cancer families.[8] The three criteria include:

1. Three or more first-degree relatives (father, brother, son),
2. Three successive generations of either the maternal or paternal lineages, and/or
3. At least two relatives affected at age 55 years or younger.

Families need to fulfill only one of these criteria to be considered to have hereditary prostate cancer. One study investigated attitudes regarding prostate cancer susceptibility among sons of men with prostate cancer.[9] They found that 90% of sons were interested in knowing if there is an inherited susceptibility to prostate cancer and would be likely to undergo screening as well as consider genetic testing if there was a family history of prostate cancer; however, similar high levels of interest in genetic testing for other hereditary cancer syndromes have not generally been borne out in testing uptake once the clinical genetic test becomes available.

Risk Assessment and Analysis

Assessment of a man concerned about his inherited risk of prostate cancer should include taking a detailed family history, eliciting information regarding personal prostate cancer risk factors, documenting other medical problems, and evaluating genetics-related psychosocial issues.

Family history documentation is based on construction of a pedigree, and generally includes:

- The history of cancer in both maternal and paternal bloodlines.
- All primary cancer diagnoses (not just prostate cancer) and ages at onset.
- Race and ethnicity.
- Other health problems including benign prostatic hypertrophy.[10]

(Refer to the Documenting the family history section in the PDQ summary on [Cancer Genetics Risk Assessment and Counseling](#) for a more detailed description of taking a family history.)

Report to Nation Finds
Declines in Cancer Incidence,
Death Rates

High Dose Chemotherapy
Prolongs Survival for
Leukemia

Prostate Cancer Study Shows
No Benefit for Selenium,
Vitamin E

The Nation's Investment in
Cancer Research FY 2009

Past Highlights

Analysis of the family history generally consists of four components:

1. Evaluation of the pattern of cancers in the family to identify cancer clusters, which might suggest a known inherited cancer syndrome. In addition to site-specific prostate cancer, other cancer susceptibility syndromes include prostate cancer as a component tumor (e.g., Hereditary Breast/Ovarian Cancer syndrome [associated with mutations in *BRCA1* and *BRCA2*]).
2. Assessment for genetic transmission. The pedigree should be assessed for evidence of both autosomal dominant and X-linked inheritance, which may be associated with a higher likelihood of an inherited susceptibility to prostate cancer. Autosomal dominant transmission is characterized by the presence of affected family members in sequential generations, with approximately 50% of males in each generation affected with prostate cancer. X-linked inheritance is suggested by apparent transmission of susceptibility from affected males in the maternal lineage. Refer to the Analysis of the Family History section in the PDQ summary on [Cancer Genetics Risk Assessment and Counseling](#) for more information.
3. Age at onset of prostate cancer in family. An inherited susceptibility to prostate cancer may be likely in families with early-onset (inconsistently defined) prostate cancer.[11] However, genetic research is also underway in families with an older age of prostate cancer onset. In the aggregate, the data are inconsistent relative to whether hereditary prostate cancer is routinely characterized by a younger-than-usual age at diagnosis.
4. Risk assessment based on family and epidemiological studies. Multiple studies have reported that first-degree relatives of men affected with prostate cancer are two to three times more likely to develop prostate cancer than are men in the general population. In some studies, the relative risk of prostate cancer is highest among families who develop prostate cancer at an early age, consistent with other cancer susceptibility syndromes where early age at onset is a common feature. It has been estimated that male relatives of men diagnosed with prostate cancer younger than 53 years have a 40% lifetime cumulative risk of developing prostate cancer.[12] A population-based case-control study of more than 1,500 cases and 1,600 controls, in which Caucasians, African Americans, and Asian Americans were studied, reported an odds ratio of 2.5 for men with an affected first-degree relative after adjusting for age and ethnicity.[13] For men with a brother and father or son affected with prostate cancer, the relative risk was estimated to be 6.4.

A number of studies have examined the accuracy of the family history of prostate cancer provided by men with prostate cancer. This has clinical importance when risk assessments are based on unverified family history information. In an Australian study of 154 unaffected men with a family history of prostate cancer, self-reported family history was verified from cancer registry data in 89.6% of cases.[14] Accuracy of age at diagnosis within a 3-year range was correct in 83% of the cases, and accuracy of age at diagnosis within a 5-year range was correct in 93% of the cases. Self-reported family history from men younger than 55 years and reports about first-degree relatives had the highest degree of accuracy.[14] Self-reported family history of prostate cancer, however, may not be reliably reported over time,[15] which underscores the need to verify objectively reported prostate cancer diagnoses when trying to determine whether a patient has a significant family history.

The personal health and risk-factor history includes, but is not limited to:

- Family history.
- Age.
- Race.
- Current and past diet history, including fat intake.
- Current and past use of drugs that can affect prostatic growth, such as steroids (e.g., finasteride [Proscar]).
- Current and past use of complementary and alternative medications (e.g., saw palmetto, PC-SPES). [16] (For more information on PC-SPES, refer to the PDQ complementary and alternative medicine summary on PC-SPES.)

The most definitive risk factors for prostate cancer are age, race, and family history.[17] The correlation between other risk factors and prostate cancer risk is not clearly established. Despite this limitation, cancer risk counseling is an educational process that provides details regarding the state of the knowledge of prostate cancer risk factors. The discussion regarding these other risk factors should be individualized to incorporate the consultand's personal health and risk factor history. (For a more detailed description of prostate cancer risk factors, refer to the Risk Factors for Prostate Cancer section of this summary.)

The psychosocial assessment in this context might include evaluation of:

- Level of psychological distress.
- Perceived risk of prostate cancer.
- Past history of depression, anxiety, or other mental illness.

One study found that psychological distress was greater among men attending prostate cancer screening who had a family history of the disease, particularly if they also reported an overestimation of prostate cancer risk. Psychological distress and elevated risk perception may influence adherence to cancer screening and risk management strategies. Consultation with a mental health professional may be valuable if serious psychosocial issues are identified.[18]

Genetic Testing

At this time, clinical genetic testing to detect inherited prostate cancer predisposition is not available. None of the candidate susceptibility genes have been unequivocally associated with prostate cancer predisposition. (Refer to the Prostate Cancer Susceptibility Loci section of this summary for more information.) For families suspected of having an inherited susceptibility to prostate cancer, participation in ongoing research studies investigating the genetic basis of inherited prostate cancer susceptibility can be considered.

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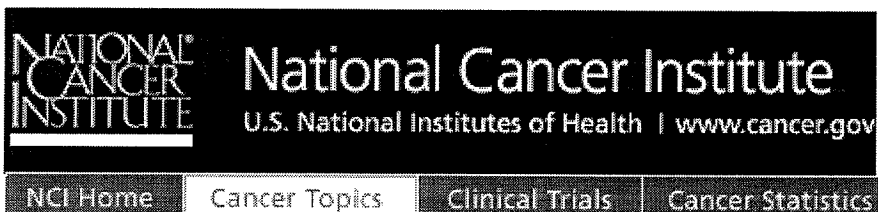
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Skin Cancer Screening (PDQ®)



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Significance

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Incidence and Mortality

Skin cancer is the most common cancer in the United States, affecting more than 1,000,000 every year. It accounts for more than 10,000 deaths annually.[1]

Skin cancers are easily detected clinically and are often cured by excisional biopsy alone. This means that they are unimportant or can be neglected without adverse consequences. When neglected, they can be disfiguring and/or cause death.

There are three major types of skin cancer: basal cell carcinoma, squamous cell carcinoma, and melanoma. Basal cell carcinoma has the highest incidence and melanoma has the lowest. Squamous cell carcinomas have an excellent prognosis, but persons diagnosed with these nonmelanomatous skin cancers are at higher risk for developing additional skin cancers.[2] Melanoma, which is the focus of this summary, accounts for approximately three-fourths of all skin cancers.

Mortality from melanoma increased after the 1970s, especially in white males.[3,4] In the 1980s, mortality rates stabilized. In 2008, it is estimated that 62,480 individuals are expected to die of melanoma, and about 8,420 are expected to die of this disease.[1] In the United States, observed mortality increased 126% between 1973 and 1995, at a rate of approximately 6% per year,[5] though it appears also to have stabilized in the 1990s.[4] A study of skin biopsy rates in relation to melanoma incidence rates obtained from the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute indicated that much of the observed increase in incidence between 1986 and 1995 was confined to local disease and was most likely caused by overdiagnosis as a result of increased screening rates during this period.[6]

Risk Factors

The incidence of melanoma rises rapidly in Caucasians after age 20 years. Fair-skinned individuals exposed to the sun are at higher risk. The best defense against skin cancer is protection from ultraviolet light, though the effectiveness of sunscreens in preventing melanoma has been questioned. (Refer to the PDQ summary on [Prevention of Skin Cancer](#) for more information.) Individuals with a history of precancerous types of pigmented lesions (dysplastic or atypical nevi), with several large nondysplastic nevi, or with moderate freckling have a twofold to threefold increased risk of developing melanoma. Individuals with familial dysplastic nevus syndrome or with several dysplastic or atypical nevi have a (>fivefold) risk of developing melanoma.[8]

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Death Rates

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Screening

Introduction

The Developmental Therapeutics Program (DTP) operates a progressive, tiered *in vitro* and *in vivo* anti-cancer compound screening program for single pure compounds with the goal of identifying and evaluating novel chemical leads and biological mechanisms of action. The program does not support screening of chemical libraries. The DTP screens include the NCI 60 cell line screen and, as appropriate, the hollow fiber assay and relevant human tumor xenograft and rodent tumor models. Information on the experimental details for the screens, the overall DTP testing paradigm, instructions on submitting compounds and the execution of confidentiality agreements with NCI can be found at the links below. Please note that DTP no longer routinely performs anti-angiogenesis evaluations. In addition, the anti-HIV screen is no longer operational although **Archival Anti-HIV Screening Data** is available. Researchers interested in NIH anti-viral screening resources are referred to the National Institute of Allergy and Infectious Diseases (NIAID) under **NIAID Resources for Researchers**.

Screening Information

In Vitro Testing

- Tumor Cell Line Screen

In Vivo Testing

- Acute Toxicity Determination
- Hollow Fiber Assay
- Tumor Xenograft Models

Anti-Cancer Screening Paradigm

- This printable chart (pdf) summarizes the DTP anti-cancer compound screening services decision tree along with a color-coded key indicating the communication method, between DTP and suppliers, for decisions and data transfer.

Discreet Screening Agreement

- Confidentiality Agreement Forms

Submission of Purified Compounds

- Instructions for submission of purified natural products and synthetic compounds for tumor cell line screening.

Screening Services

Cell Lines In The *In Vitro* Screen

Note: This is a list of the 60 human cancer cell lines used in the screen and maintained at NCI-Frederick. Additional lines evaluated for use in the screen and currently available are listed separately at the bottom of the page.

Please note the links for more information on the SNB-19, U251, NCI/ADR-RES, and MDA-MB-435 cell lines.

- MDA-MB-435
- U251
- SNB-19
- NCI/ADR-RES

Cell Line Name	Panel Name	Doubling Time	Inoculation Density
CCRF-CEM	Leukemia	26.7	40000
HL-60(TB)	Leukemia	28.6	40000
K-562	Leukemia	19.6	5000
MOLT-4	Leukemia	27.9	30000
RPMI-8226	Leukemia	33.5	20000
SR	Leukemia	28.7	20000
A549/ATCC	Non-Small Cell Lung	22.9	7500
EKVX	Non-Small Cell Lung	43.6	20000
HOP-62	Non-Small Cell Lung	39	10000
HOP-92	Non-Small Cell Lung	79.5	20000
NCI-H226	Non-Small Cell Lung	61	20000
NCI-H23	Non-Small Cell Lung	33.4	20000
NCI-H322M	Non-Small Cell Lung	35.3	20000
NCI-H460	Non-Small Cell Lung	17.8	7500
NCI-H522	Non-Small Cell Lung	38.2	20000
COLO 205	Colon	23.8	15000
HCC-2998	Colon	31.5	15000
HCT-116	Colon	17.4	5000
HCT-15	Colon	20.6	10000
HT29	Colon	19.5	5000
KM12	Colon	23.7	15000
SW-620	Colon	20.4	10000
SF-268	CNS	33.1	15000
SF-295	CNS	29.5	10000
SF-539	CNS	35.4	15000
SNB-19	CNS (For more Information)	34.6	15000

SNB-75	CNS	62.8	20000
U251	CNS (For more information)	23.8	7500
LOX IMVI	Melanoma	20.5	7500
MALME-3M	Melanoma	46.2	20000
M14	Melanoma	26.3	15000
MDA-MB-435	Melanoma (For more information)	25.8	15000
SK-MEL-2	Melanoma	45.5	20000
SK-MEL-28	Melanoma	35.1	10000
SK-MEL-5	Melanoma	25.2	10000
UACC-257	Melanoma	38.5	20000
UACC-62	Melanoma	31.3	10000
IGR-OV1	Ovarian	31	10000
OVCAR-3	Ovarian	34.7	10000
OVCAR-4	Ovarian	41.4	15000
OVCAR-5	Ovarian	48.8	20000
OVCAR-8	Ovarian	26.1	10000
NCI/ADR-RES	Ovarian (For more information)	34	15000
SK-OV-3	Ovarian	48.7	20000
786-0	Renal	22.4	10000
A498	Renal	66.8	25000
ACHN	Renal	27.5	10000
CAKI-1	Renal	39	10000
RXF 393	Renal	62.9	15000
SN12C	Renal	29.5	15000
TK-10	Renal	51.3	15000
UO-31	Renal	41.7	15000
PC-3	Prostate	27.1	7500
DU-145	Prostate	32.3	10000
MCF7	Breast	25.4	10000
MDA-MB-231/ATCC	Breast	41.9	20000
HS 578T	Breast	53.8	20000
MDA-N Not Available	Breast	22.5	15000
BT-549	Breast	53.9	20000
T-47D	Breast	45.5	20000

Additional Lines

Cell Line Name	Panel Name	Doubling Time	Inoculation Density
LXFL 529	Non-Small Cell Lung		10000

DMS 114	Small Cell Lung		20000
SHP-77	Small Cell Lung		40000
DLD-1	Colon		50000
KM20L2	Colon		10000
SNB-78	CNS		20000
XF 498	CNS		20000
RPMI-7951	Melanoma		20000
M19-MEL	Melanoma		10000
RXF-631	Renal		10000
SN12K1	Renal		10000
MDA-MB-468	Breast		20000
P388	Leukemia		50000
P388/ADR	Leukemia		50000